pages 28 and 34 to 43 of the Application. The subject matter of Claim 12 is found specifically at page 35 of the Application as filed.

Applicants propose to deal with the Examiner's grounds for rejection and the objections made by the Examiner in the order set out in the Official Action dated July 14, 1994.

Double Patenting

The Examiner has provisionally rejected Claims 6 to 20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over specified Claims of Applicants' other pending Applications. The Examiner readily admits that the conflicting claims are not identical. With the amendments made to this Application and that have been made or will be made to the Claims of Application Serial No. 07/675,908, 08/018,508 and 08/018,754, Applicants submit that the double patenting issue may not arise. If the double patenting issue when claims are allowed, is of concern to the Examiner, Applicants will file appropriate terminal disclaimers as required. Furthermore, Applicants wish to advise the Examiner that U.S. Application Serial No. 07/675,908 is the National Entry Application from Applicants' PCT Application (PCT/CA90/00306) and had a Publication Number WO-A-91/04058. This Application 07/838,675 and Applications 08/018,508 and 08/018,754 comprise subject matter that is taught in PCT Application PCT/CA93/00062 (Applicants' Agent's File PC-1022). PCT/CA93/00062 was examined by the PCT Offices and a Notification of Transmittal of International Preliminary Examination Report was issued by the Examiner in respect of the claims attached to the report. The Examiner found that the subject matter claimed in the claims

attached to the Notification of Transmittal of International Preliminary Examination Report were allowable over and above Applicants' prior published Application Serial No. PCT/CA90/00306 (which bore an International Publication No. WO-A-91/04058). Applicants will therefore, at an appropriate time, submit to the Examiner that the subject matter in this Application is patentably distinct over and above Application 07/675,908. However, terminal disclaimers may have to be filed with respect to co-pending Applications 08/018,508 and 08/018,754 which claim also to be continuations in part of Application 07/675,908. Copies of PCT Application PCT/CA93/00062 and the Notification of Transmittal of International Preliminary Examination Report in respect of that Application are attached as **Schedules A and B** of this Response.

Oath and Declaration

Applicants have reviewed the comments of the Examiner under the heading Oath/Declaration. In the March 5, 1993 Response, Applicants followed the suggestion of Examiner Nutter that the Application be made a continuation-in-part of Application Serial No. 675,908 and which claimed priority from Canadian Application Serial No. 613,307 filed September 21, 1989. In the Voluntary Amendment dated March 5, 1993, Applicants requested in the Disclosure at page 1, line 3 before Field of Invention, that the following be inserted:

> "This Application is a Continuation-In-Part Application of United States Patent Application Serial Number 07/675,908 filed on July 3, 1991 which application was the application entering

the National Phase in the United States from PCT Application Serial Number PCT/CA90/00306 which application claims priority from Canada {sic} Patent Application Serial Number 612,307-4 filed September 21, 1989."

If the said requested insertion has not been made, the Examiner is now requested to do so. He should have regard to the Voluntary Amendment dated March 5, 1993. In the Response also dated March 5, 1993 to the Official Action relating to the Election of Inventions, the Applicants enclosed two documents, each entitled "Declaration, Power of Attorney, and Petition" executed by Drs. Rudolf Edgar Falk and Samuel Simon Asculai which referred to the Canadian Patent Application Serial No. 2,061,566 from which Applicant claimed convention priority and referred in the said Declaration, Power of Attorney, and Petition to the earlier filed United States Patent Application 07/675,908 from which it claimed the Application was a continuation-in-part application. (Applicants also enclosed a certified copy of Canadian Application 2,061,566 from which priority was claimed.)

If the Applicants have inadvertently improperly completed these two documents each entitled "Declaration, Power of Attorney, and Petition", then the Examiner is requested to assist the Applicants by advising what changes should be made. If however, Applicants have correctly completed these documents, the Examiner is requested to acknowledge <u>on a revised filing receipt</u> the priority claimed under 35 U.S.C. § 119 and priority under 35 U.S.C. § 120. Applicants enclose a copy of the Declaration, Power of Attorney, and Petition of both Drs.

Falk and Asculai as **Schedules C and D** hereto that were filed with the March 5, 1993 Voluntary Amendment. The Examiner is thanked for his consideration in this regard.

Claim Rejections - 35 U.S.C. § 101

The Examiner has rejected Claims 6 to 20 because the invention disclosed, according to the Examiner, is inoperative and lacks utility. The Examiner's position is that eight uncontrolled, unblinded, non-randomized case studies is insufficient (according to him) to assert the utility of the composition having regard to Kelley et al which discusses the spontaneous complete regression of basal cell carcinoma in a patient having regard to Type III Transepithelial Elimination. The Examiner refers to page 892 in the Official Action but the Kelley article enclosed is found on pages 1039 to 1042. (Applicants are confused.) Applicants respectfully dispute the Examiner's conclusions and discuss the reasons why these examples are sufficient. Further Applicants' additional material enclosed herewith further rebuts the Examiner's position. This additional material is submitted without in any manner acquiescing to the Examiner's position but to assist the Examiner further that Applicants' invention has in fact utility. Firstly, Applicants refer the Examiner to **Schedule A** at pages 70 to 72 and Figures 1 (a), 1 (b), 2 (a), 2(b), 3 (a) to 3(d), 4 (a) to 4 (d), 5 (a) to 5 (d), 6 (a) to 6 (c). (Figure 7 deals with tumours in the skin.) The Examiner will note that with reference to Figure 5 that the male, age 86 could reach his temple for the application of the formulation containing HA and NSAIDS but not his back (see lines 31 to 40 of page 71 and page 72, lines 1 to 3). The basal cell carcinoma was after continuous application disappearing on the gentleman's temple and forehead but not

on his back where it continued to grow. This gentleman acted as his own control. In view of this example alone, it is clear that the rejection under 101 is unfounded. When coupled to the other examples, the conclusion is overwhelming that the rejection is unfounded.

Additionally, Applicants enclose for the Examiner's review Press Releases of Hyal Pharmaceutical Corporation (previously licensee of this invention, now assignee of the application) which releases identified to the public that of the Phase III trials, an 87% response rate in respect of the treatment of basal cell carcinoma. Applicants enclose a copy of a brief write-up of the tests conducted with respect to the treatment of basal cell carcinoma that is referred to in the Press Release. The Press Release is attached as **Schedule E**. The formulation used in the tests is formulation 3 referred to at page 36. Applicants also enclose two other write-ups of results of administering Applicants' invention for the treatment of basal cell carcinoma as follows: "A Novel Approach to the Treatment of Supeficial Basal Cell Carcinoma" - **Schedule F** and "A Novel Topical Therapy for Treatment of Superficial Basal Cell Carcinoma" - **Schedule F1.**

Applicants are prepared to provide suitable Affidavit Evidence attaching this material to corroborate this information provided herein if the Examiner feels a need for same. However, Applicants do not acquiesce in the conclusions of the Examiner under 35 U.S.C. § 101. In Applicants respectful submission, the specification as filed need not establish that the remission incidence observed post-treatment is greater than what would be expected spontaneously. That is not what is required in law. A disclosure which contains representative

examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim will possess the alleged utility is all that is required when there is no reason to suspect the assertions are not accurate. See In re Barr (CCPA, 1971) 444 F2d 558, 170 USPQ 330. Nothing is gained by repetitive examples which each assert the same kind of activity for the composition embraced by the claim. See In re Surrey (CCPA, 1966) 370 F2d 349, 151 USPQ 274. The Examiner, by submitting the article by Kelley et al attempts to cast doubt with respect to Applicants' examples thereby implying that all examples in which the persons were successfully treated for basal cell carcinoma after being treated with the Applicants' treatment, spontaneously cured themselves by going into spontaneous remission. This is hardly probable having regard to the teachings in the Application as a whole. At page 1, line 21 Applicants advise that basal cell carcinoma is presently being treated by surgery. Each lesion together with all surrounding and underlying tissue (dermis, epidermis, and sub-dermis) is cut out. Because of the position of the basal cell carcinoma (many times on the face of the patient because of extensive exposure to the sun) the resection may jeopardize the patient's health. In this regard, see the examples, particularly examples 3 and 6. In example 6, the male patient was first treated for the basal cell carcinoma by an oncologist who attempted to surgically excise the lesion without success and then irradiated the lesion again without success. However, when treated by Applicants' formulation (diclofenac with sodium hyaluronate and excipients) the lesion disappeared. Is this spontaneous regression? Hardly likely. This successful resolution was clearly the result of using Applicants' formulation. In fact, as stated at example 6 at page 55:

> "This resolution clearly indicates that even with prior applications of unsuccessful therapies (surgery and irradiation) Applicant's {sic} formulations can be used successfully."

This example alone would be sufficient to rebut the Examiner's conclusions. Coupled with the other examples, the evidence is overwhelming. Reconsideration of the Examiner's conclusions is respectfully requested.

Claim Rejections - 35 U.S.C. § 112

The Examiner takes the position under 35 U.S.C. § 112 that the disclosure is limited to the use of hyaluronic acid or sodium hyaluronate.

Applicants respectfully traverse this conclusion. Sodium hyaluronate is a pharmaceutically acceptable salt of hyaluronic acid. Persons skilled in the art would know to use or substitute other pharmaceutically acceptable salts of hyaluronic acid in Applicants' invention. Applicants respectfully submit that the disclosure in the Application is addressed to persons skilled in the art and such persons would have no difficulty choosing the pharmaceutically acceptable salts.

Further, without acquiescing to any of the conclusions or grounds by the Examiner for his rejection of the other forms of hyaluronic acid for example, homologues, analogues, derivatives, complexes, esters, fragments, and subunits, Applicants have, in this Response, (but not for

any Continuation Application, Continuation-in-Part Application, Divisional Application, or any Re-Issue Application of any Patent issuing from this Application) amended the Claims to delete homologues, analogues, derivatives, complexes and esters to advance the prosecution of this Application. However, Applicants have not deleted fragments and subunits as the fragments and subunits are merely smaller molecular weights of hyaluronic acid. The smaller units are the same thing.

Additionally, with respect to the Examiner's submission that the enabling disclosure only supports hyaluronic acid or sodium hyaluronate, Applicants wish to draw the Examiner's attention to the fact that with respect to all the various forms of hyaluronic acid, no data need be included in the Application showing that all these forms have the asserted utility.

The first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement. Whether this is achieved by the use of illustrative examples or by broad terminology is of no importance. In re Marzocchi et al. (CCPA 1971) 439 F2d 220, 169 USPQ 367. An assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. In re Dinh-Nguyen et al., (CCPA 1974) 492 F2d 856, 181 USPQ 46; In re Bowen, (CCPA 1974) 492 F2D 859M 181 USPQ 48; In re Armbruster (CCPA 1975) 512 F2d 676, 185 USPQ 152. Della Valle and Seifter do nothing to support the Examiner's conclusions).

There is not a fixed number of compounds which must be named or examples given to provide adequate support for a broad Claim, since such number varies, depending on the circumstances of the particular case. In re Shokal et al., (CCPA 1957) 242 F2d 771, 113 USPQ 283.

The number and variety of examples is irrelevant if the disclosure is "enabling" and sets forth the "best mode contemplated". In re Borkowski et al. (CCPA 1970) 442 F2d 904, 164 USPQ 642. A disclosure which contains representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a Claim will possess the alleged utility is all that is required, when there is no reason to suspect the assertions are not accurate. In re Barr et al. (CCPA 1971) 444 F2d 558, 170 USPQ 330. Nothing is gained by repetitive examples which each assert the same kind of biological activity for every compound embraced by the Claim. In re Surrey (CCPA 1966) 370 F2d 349, 151 USPQ 724. An applicant need not provide a specific example of everything embraced by a broad Claim. In re Anderson (CCPA 1973) 471 F2d 1237, 176 USPQ 331. Each Claim need not be supported by a specific example. Ex parte Morey (POBA 1944) 66 USPQ 191.

Although at one time the Patent Office required at least one "working" example as part of the disclosure of the specification, there is no absolute statutory requirement for such an example if the disclosure is such that one skilled in the art can practise the claimed invention. In re Bordowski et al. (CCPA 1970) 422 F2d 904, 164 USPQ 642; Ex parte Nardi et al. (BPAI 1986) 229 USPQ 79. Use of "prophetic" examples does not automatically make a patent non-enabling merely because there can be no guarantee that the examples would actually

work. Atlas Powder Co. v. E.I. DuPont de Nemours & Co. (CAFC 1984) 750 F2d 1569, 224 USPQ 409.

Although a specification preferably should contain a "working" example to ensure that the "how to make and use" and "best mode" requirements of 35 USC 112 are met, a working example is not mandatory if none actually exists and the invention is otherwise disclosed so that one skilled in the art can practice it without undue experimentation. In re Borkowski et al. (CCPA 1970) 422 F2d 904, 164 USPQ 642; In re Gay (CCPA 1962) 309 F2d 769, 135 USPQ 311; In re Stephens et al. (CCPA 1976) 529 F2d 1343, 188 USPQ 649; Ex parte Krenzer (POBA 1978) 199 USPQ 227. Since 35 USC 112 does not demand a "working example", an application cannot be fatally defective merely because it lacks one. In re Long (CCPA 1966) 368 F2d 892, 151 USPQ 640; In re Honn et al. (CCPA 1966) 364 F2d 454, 150 USPQ 652. In re Bartholome et al. (CCPA 1967) 386 F2d 1019, 156 USPQ 20; Ex parte Kenaga (POBA 1974) 189 USPQ 62. The patent and Trademark Office has the burden of showing that the disclosure entails undue experimentation. In re Angstadt (CCPA 1976) 537 F2d 498, 190 USPQ 214.

Applicants' disclosure of their invention is addressed to persons skilled in the art. You, the Examiner, in light of the above submissions have the burden of showing that the disclosure does not teach an invention or how the invention is to be used. You have the burden. Applicants respectfully submit this burden has not been overcome. In this regard, the Application is very clear. Furthermore, human testing is not always required to establish the utility of a claimed compound or composition whose intended use is to include human consumption. See

Carter-Wallace Inc., and Riverton Laboratories Inc., (SDNY 1969) 304 FSupp 357, 164 USPQ 73; In re Langer (CCPA1974) 503 F2d 1380, 183 USPQ 288.

Because the onus is on the Examiner and because Applicants' subsequent application **(Schedule A)** and additional test material refutes and negates the Examiner's objections and conclusions, Applicants respectfully traverse the objections of the Examiner.

In Applicants' respectful submission Applicants assertions for the remaining forms of hyaluronic acid are believable on their face and are straight forward. There is no reason to challenge Applicants' inclusion of these forms.

In view thereof, Applicants respectfully submit that the disclosed utility of all forms must be accepted as accurate. See In re Gazave (CCPA 1967) 379 F2d 973 154 USPQ 92; In re Bundy, (CCPA 1981) 642 F2d 430, 209 USPQ 48.

The above comments apply equally to the disclosure as to the Claims.

In the interests of advancing the prosecution of the Application, as previously advised and on the basis given, Applicants have amended the forms of hyaluronic acid in the claims to hyaluronic acid, pharmaceutically acceptable salts, fragments, and subunits. The term "pharmaceutically acceptable salts thereof" does not encompass a large number of components and in fact would be readily understood by persons skilled in the art. The salts are referring to pharmaceutically

acceptable salts of hyaluronic acid. These salts do not require an undue amount of experimentation.

The Examiner will note that Applicants' molecular weights and use of higher molecular weights and amounts referred to in the Claims clearly are treated differently than Della Valle. The Examiner will also appreciate when he reviews the response to the 103 rejection that Seifter does not teach the use of hyaluronic acid or salts. The Examiner is invited to read page 3, right-hand column, lines 45 to 47 of Seifter.

> "Undepolymerized hyaluronic acid (HA) had practically no useful spreading effect, as compared with the control of Table II."

Whatever "spreading effect" means within the meaning of the Seifter reference, hyaluronic acid is not suitable thus clearly teaching away from Applicants' invention. In any event, Applicants' have provided sufficient direction and guidance to the persons skilled in the art to select properly or administer the hyaluronic acid, pharmaceutically acceptable salts, fragments and subunits without undue experimentation.

The Examiner also objects to Claims 11, 15, and 20 and the amount of hyaluronic acid or salt thereof in excess of 50 to 60 mg per dosage because the Claims read "on any amount up to and including infinity". Applicants have amended the Claims so as to restrict the Claims to an effective dosage amount comprising at least about 50 to 60 mg of the form of hyaluronic acid. Applicants respectfully submit that this amendment is sufficient to overcome the rejection of the

Examiner. In any event, the Claims are addressed to persons skilled in the art and persons skilled in the art would not use an unreasonable amount at any time when applying the formulation. Exemplary formulations are taught in the Application from which dosage amounts can be taken and the dosage amounts are exemplified in the Claims. Applicants respectfully submit that the Examiner should withdraw the rejections under 35 U.S.C. § 112.

Claim Rejections - 35 U.S.C. § 103

Dealing now with the Examiner's rejection of Applicants' Application under 35 USC 103, Applicants respectfully submit that their invention is clearly not obvious. In fact the teachings of the prior art cited by the Examiner and brought to the Examiner's attention through the Information Disclosure Statement previously submitted and the later Supplementary Information Disclosure Statement now being submitted teach in different directions from Applicants' invention, teach away from Applicants' invention and thus, clearly establish the patentability of Applicants' invention. Thus, the Claims of the invention are clearly patentable.

(Applicants enclose a Supplementary Information Disclosure Statement referring to a substantial number of additional references which Applicants submit that the Examiner will find are not pertinent. Copies of these items were previously submitted to the Examiner with Application Serial No. 07/675,908 with the respective Response filed January 6, 1995 and are therefore not included with this Supplementary Information Disclosure Statement. In addition, one sheet of Form PTO-

1449 listing them, are submitted herewith pursuant to 37 C.F.R. §§ 1.97-1.99 and to the duty of disclosure set forth in 37 C.F.R. § 1.56.)

Before, however, embarking on a discussion of the actual references cited by the Examiner, Applicants wish to bring the following statement of the law as it applies to Applicants' invention to the Examiner's attention. Particularly, the motivation for combining the teachings of references for a finding of obviousness under 35 USC 103 must be inherent (must be within) the teachings of the prior art and the specific references cited by the Examiner. In other words, the references must themselves form a basis for establishing that specific prior art can be combined and is meant to be combined with other references. Finally, even if the prior art teaches combinations (for example, of medicines which inhibit prostaglandin synthesis with a form of hyaluronic acid which is denied) but the results of the Applicants' combination in the amounts specified in the Applicants' Claims yield unexpected results, totally unexpected from those expected by the combinations in the prior art, then the invention is unobvious because persons skilled in the art would not expect the results achieved by Applicants. And that is precisely what Applicants have achieved. This is clear from the teachings of Applicants' Application and from the additional test results provided to the Examiner.

In this regard the Examiner's attention is directed to In re Laskowski 10 USPQ 2d 1397. In that case the Court of Appeals, Federal Circuit held that

"Although the Commissioner suggest that Hoffman could readily be modify to form the Laskowski structure, "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification". In re Gorden, 733 F2d 900, 902, 221 UAPQ 1125, 1127 (Fed. Cir. 1984), In re Sernaker, 702 F2d 989, 994, 217 USPQ 1, 5 (Fed. Cir. 1983).

The prior does not suggest Laskowski's modification of the Hoffman band saw wheel, or provide any reason or motivation to make that modification. In re Regal, 526 F2d 1399, 1403 n.6, 188 USPQ 136, 139 n.6 (CCPA 1975) ("there must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references") (citing In re Stemniski, 44 F2d 581, 170".

In other words Hindsight is 20/20 and that is precisely the Examiners' view point. Having purported to have found "bits and pieces" of Applicants' invention in the prior art, the Examiner has combined the references without motivation. No persons reading the prior art would be motivated to develop Applicants' formulations or any of Applicants' formulations from the prior art teachings.

In order for a combination of references to render an invention obvious, it must be apparent that their teachings can be combined. In re Avery (CCPA 1975) 518 F2d 1228, 186 USPQ 161. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teachings, suggestion or incentive supporting the combination. In re Geiger (CAFC 1987) 815 F2d 686, 2

PQ2d 1276; In re Fine (CAFC 1988) 837 F2d 1071, 5 PQ2d 1596. When the incentive to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper. Ex parte Skinner (BPAI 1986) 2 PQ2d 1788. The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination, Berghauser v. Dann. Comr. Pats. (DCDC 1979) 204 USPQ 393; ACS Hospital Systems, Inc. v. Montefiore Hospital (CAFC 1984) 732 F2d 1572, 221 USPQ 929. Citing references which merely indicate that isolated elements and/or features recited in the Claims are known is not a sufficient basis for concluding that the combination of Claimed elements would have been obvious. Ex parte Hiyamizu (BPAI 1988) 10 PQ2d 1393. The same conclusion is true where the references expressly teach away from what the PTO contends is obvious from the references, In re Grasseli et al. (CAFC 1983) 713 F2d 731, 218 USPQ 769, or, where the examiner's proposed modification would render the prior art version unsatisfactory for its intended purpose. Ex parte Rosenfeld (POBA 1961) 130 USPQ 113. Accord, In re Gordon, 733 F2d 980, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); In re Kramer (CAFC 1990 Unpublished decision) 18 PQ2d 1415. The references, viewed by themselves and not in retrospect, must suggest doing what applicants have done. In re Shaffer ()CCPA 1956) 229 F2d 476, 108 USPQ 326, In re Skoll (CCPA 1975) 523 F2d 1392, 187 USPQ 481.

The mere fact it is possible for two isolated disclosures to be combined does not render the result of that combination obvious absent a logical reason of record which justifies the combination. In re Regel et al. (CCPA 1975) 526 F2d 1399, 188 USPQ 136. To properly combine

two references to reach a conclusion of obviousness, there must be some teachings, suggestion or inference in either or both of the references, or knowledge generally available to one of ordinary skill in the art, which would have led one to combine the relevant teachings of the two references. Ashland Oil Inc. v. Delta Resins and Refractories, Inc. et al. (CAFC 1985) 776 F2d 281, 227 USPQ 657; 5 PQ2d 1532. Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be founded in the prior art, not in Applicants' disclosure. In re Vaeck (CAFC 1991) 20 USPQ F2d 1438.

The mere allegation that the differences between the claimed subject matter and the prior art are obvious does not create a presumption of unpatentability which forces Applicants to prove conclusively that the Patent Office is wrong. In re Soli (CCPA 1963) 317 F2d 941, 137 USPQ 797. The ultimate legal conclusion of obviousness must be based on facts or records, not on the Examiner's unsupported allegation that a particular structural modification is "well known" and thus obvious. Subjective opinions are of little weight against contrary evidence. In re Wagner et al. (CCPA 1967) 371 F2d 877, 152 USPQ 552. If the examiner seeks to rely upon a theory of chemistry for obviousness, he must provide evidentiary support for the existence and meaning of that theory. In re Grose et al. (CCPA 1979) 592 F2d 1161, 201 USPQ 57. Unless the Applicants question the accuracy of a statement of the Examiner unsupported by the art of record (for example by requesting a Rule 107 affidavit), or by presenting evidence to contradict it, it will probably be accepted as true on appeal. In re Shapleigh (CCPA 1957) 248 F2d 96, 115 USPQ 129; In re Lundberg et al. (CCPA 1957) 244 F2d 543, 113 USPQ 530 MPEP

706.02(a). Data in the specification showing the claimed article possesses characteristics not possessed by the prior art should be accepted as accurate, notwithstanding the contrary opinion expressed sua sponte by the Board of Appeals. In re Ehringer (CCPA 1965) 347 F2d 612, 146 USPQ 31, (shock-resistant, vibration-resistant and non-sag filament wire...).

The Examiner has only provided theory in his rejections. No basis for his statements of obviousness have been provided. While the prior art references purport to relate to forms for hyaluronic acid, they do not teach Applicants' methods or specific embodiments claimed. If the Examiner relies on personal knowledge when combining these references, then he must advise Applicants. If this is not the case, then there is no clear teaching of Applicants' invention including the method claims in any of the combinations of the prior art. Most importantly, nor is there any motivation from these references to develop Applicants' invention. Because the Examiner's conclusions are not supported by the prior art, the Examiner is requested to verify his conclusions (as for example, by Affidavit).

Referring specifically to the prior art, the Examiner in rejecting the Claims, has relied on Seifter, U.K. Patent 769,287 read in view of the teachings of Schultz, U.S. Patent 4,808,576, Miyazaki Japanese Application 116678/88 and Della Valle et al., U.S. Patent 4,736,024.

The main reference relied on by the Examiner is U.K. Patent 769,287 (Seifter). This patent teaches the use of partially depolymerized hyaluronic acid (PDHA) - not hyaluronic acid, salts thereof, fragments or subunits or even homologues, analogues,

derivatives, complexes, esters or any other form of hyaluronic acid. The form of hyaluronic acid is partially depolymerized and is termed PDHA. The PDHA is said to be purportedly useful as a spreading agent and lipemia-clearing agent (page 1, left-hand column, lines 14 to 15) and purportedly useful to facilitate the spread and absorption of injected materials in animals and human tissues. (page 1 of patent, left-hand column, lines 37 to 39), (lipemia, Applicants submit, means excessive lipids in the blood). The patent states that this effect is a function of the degree of depolymerization and that it can be employed in drug injections and living tissues (same page, same column, line 39 to 42). Methods are provided which teach the method of manufacture of PDHA by incubation. Longer incumbation in the process of manufacture reduces the spreading effect (page 2, left-hand column, lines 8 to 10). PDHA is compared to hyaluronidase (not hyaluronic acid) which is also asserted to be an effective spreading agent but is purported to have benefits over hyaluronidase. It is therefore clear that spreading does not mean that there is any transport of the agent and penetration. In other words, everything is, as stated, absorbed. Thus, the PDHA is not active in the transport. It is passive. This conclusion is easily recognized by the statement at (page 1, left-hand column, line 38) where the "(PDHA) facilitates the spread and absorption of injected materials". In other words, oil spreads over water but does not penetrate. Material dissolved in the oil could be absorbed into the water. Thus, there would be a depot effect. However, more importantly, this reference is completely irrelevant to hyaluronic acid, pharmaceutically acceptable salts thereof, and subunits and fragments thereof. At page 3, right-hand column, lines 45 to 47, the patent provides:

"Undepolymerized hyaluronic acid (HA) had practically no useful spreading effect as compared with the control of Table II."

It is therefore, clear that this patent teaches away from the use of hyaluronic acid to transport and cause penetration of any Medicine or therapeutic agent. Whatever is meant by the term "spread" in the patent, the word "spread" has no relation to hyaluronic acid. Thus, this patent is irrelevant. This patent provides no motivation for any person skilled in the art to use hyaluronic acid. This reference states that hyaluronic acid has no practical utility in respect of spreading whatever that may mean. (Applicants' position is that spreading has nothing whatsoever to do with transport and penetration.) The '287 patent was published in 1957 some 35 years before Applicants' application.

The Examiner additionally relies on U.S. Patents 4,808,576, the Japanese Application 116678/88 and Della Valle et al U.S. Patent 4,736,024. None of these references provide any teachings of Applicants' invention by themselves (as the Examiner has already determined) because the Examiner is relying on obviousness (35 USC 103 as opposed to 102); nor do these references provide any teachings when viewed together.

U.S. Patent 4,808,576 purports to teach a discovery that hyaluronic acid will be carried to traumatized tissue by a mammal's natural processes if applied at a site remote from the traumatized tissue. In other words, if you inject the material into the blood,

somehow it will, at some lesser concentration, find its way (i.e. part of the dosage will find its way) via the blood to the site of trauma. That is the same as saying that blood pumped by the heart will find its way to the feet. This patent fails to teach Applicants' invention. Schultz further teaches that hyaluronic is the active and the carriers are the salicylates - not NSAIDS. The salicylates enumerated (see column 6, lines 1 to 18) are carriers. See the enclosed excerpts of Merck Index as **Schedules G and H**. They are not NSAIDS.

Miyazaki et al, Japanese Application 116,678/88 is to the same affect as Della Valle's U.S. Patent 4,736,024 which '024 patent is part of a group of patents and applications filed around the world. Applicants referred to the Della Valle and Fidia patents and applications and the teachings thereof in their Information Disclosure Statement and Supplementary Information Disclosure Statement.

Fidia's European Patent Application 0265116 (like its corresponding U.S. Patents) purports to teach cross-linked esters of hyaluronic acid as a substitute for hyaluronic acid in all known applications for hyaluronic acid. Thus these references purport to propose the use of cross-linked esters of hyaluronic acid for the preparation of pharmaceuticals for medicaments and particularly medicaments for local or topical use, especially in ophthalmology (page 7, line 33):

> "where they show particular compatibility with the corneal epithelium and are therefore very well tolerated, with no sensitization effects."

In apparent reference to purported prior art, this Fidia European Patent Application, at page 7, line 53, states:

> "A vast range of therapies involving chemical agents are used, administered both by topical route (often associated with steroid anti-inflammatory agents), and systemic route, such as: tetracycline, such as oxytetracycline, penicillin, such as cloxacillin and benzy penicillin, sulphamidics, polymixin B (associated with miconazole and prednisolone), chloramphenicol, tylosin and chloromycetin. Topical treatment of the disease, despite its apparent simplicity, is still an open problem, since with the ocular preparations used until now it has not been possible for one reason or another to obtain concentrations of therapeutically effective antibiotics or sulphamidics in the lachrymal secretion."

The medicaments taught are thus purported to be useful in ophthalmology, dermatology, and by analogy, in various fields of medicine which may be treated by local topical applications, for example by rectal action (see page 8, line 42). However ineffective amounts are taught.

European Patent Application 0 197 718 (like Della Valle U.S. 4,736,024) purports to disclose new medicaments for topical use, especially in dermatology and diseases of the mucous membranes. At page 2 the Application provides:

"The advantages for therapy using the medicaments according to the present invention are due to a more efficient vehicle for the drugs promoted by the acidic polysaccharide of the hyaluronic acid component and to a better bioavailability of the active substance as compared obtainable with known pharmaceutical formulations. Furthermore, the new medicaments of the invention assume particular importance in the case of ophthalmic medicaments, because due to the above mentioned qualities, there is an additional special compatibility with the corneal epithelium and, therefore, a very high level of tolerability, with no sensitization effects. When the medicaments are administered in the form of concentrated solutions with elastic-viscose characteristics or in solid form, it is possible to obtain films on the corneal epithelium which are homogeneous, stable, perfectly transparent, and which adhere well, guaranteeing prolonged bioavailability of the drug, thereby forming excellent preparations with retard effect."

At page 3, this patent application includes the same statements found at page 7, line 53 of European Application 0265116 relating to the prior art. The patent application then provides that the prior art medicaments,

> "do not have the qualities necessary for adhering to the surface of the cornea, as they do not usually have a sufficiently high concentration of active substance and cannot achieve perfect distribution (i.e., the presence of a distribution gradient)."

The patent Application discusses at page 4 that these deficiencies have been described in other prior art publications. The Application continues at page 4 purporting to describe the vehicles taught in the application for ophthalmic drugs which allows for the formulation of preparations free from concentration gradients of the active substance and, therefore, perfectly homogeneous, transparent and adhesive to the corneal epithelium, without sensitization effects, with vehicling of the active substance and possibly with a retard effect. The inventors then proceed to state that because the above-mentioned properties have uses in other fields they may be applied in dermatology and in diseases affecting the mucous membrane, such as in the mouth, for instance in odontology. In the same manner, they may also be used, the inventors allege, to obtain a systemic effect due to the effect of transcutaneous reabsorption of the medicine, for instance in suppositories. (See page 5.) The Application discusses the use of hyaluronic acid as a vehicle for use in association with a pharmaceutical substance to provide an improved drug delivery system. However, the drug delivery system is essentially for topical application without, as previously discussed herein, any transdermal and/or penetrating effect (no appropriate dosage amounts are taught). This is consistent with the teachings at page 17 of the reference wherein the

inventors discuss quantitative ratios by weight of the vehicle and pharmaceutical substance:

> "The quantitative ratios by weight of the two components (1) and (2) according to the invention may vary within ample limits and this naturally depends also on the nature of the two components and in the first case on that of the active substance. Such limits are for example the ratios of 0.01:1 and 100:1 between the two components (1) and (2). The range of variation however is preferably between the limits of 0.01:1 and 10:1 for the two said components and especially between 0.01:1 and 2:1."

The use of a broad ratio clearly does not teach any facilitation of the immediate transport of any medication.

At page 64, the inventors discuss the stability of corneal films of hyaluronic acid and pilocarpine derivatives, stating at page 65:

> "The derivatives of hyaluronic acid with pilocarpine produce a stable corneal film for periods of more that 2 hours. Transcorneal penetration of pilocarpine seems therefore to depend on the capacity of hyaluronic acid to vehicle the drug forming a homogeneous and stable film on the cornea."

At page 66, a vehicle of hyaluronic acid containing triamcinolone is described for administration in the eyes. At page 67 the inventors

concluded from the tests that the use of the hyaluronic acid sodium salt Hyalectin fraction together with triamcinolone phosphate reduces intraocular inflammation observed at the above-mentioned times compared to the administration of triamcinolone phosphate alone. This teaching relates to the film of hyaluronic acid adhering to the eye providing prolonged bioavailability of the medicine. (U.S. Patent 4,736,024 is to the same effect.)

European Patent Application 0216453 is of similar effect; esters of hyaluronic acid or one of its salts are used as vehicles for active pharmaceutical substances. At page 25 the Application discusses the use of the hyaluronic esters as vehicles for drugs to be applied topically because they are "perfectly transparent and adhesive on the corneal epithelium, guaranteeing prolonged bioavailability of the drug and therefore representing excellent preparations with a retard effect."

At page 27 the Application teaches:

> "With the esters of the present invention these difficulties can be overcome. The presence of the hyaluronic acid ester as a vehicle for ophthalmic drugs in fact allows the formulation of excellent preparations with no concentration gradients of the active substance and they are therefore perfectly homogeneous, with perfect transparency and excellent adhesiveness to the corneal epithelium, with no sensitization effects, the excellent vehicling of the active substance and possibly a retard effect."

This Application also purports to teach that the new medicaments may be exploited in fields other than ophthalmology, for example

dermatology and diseases of the mucous membranes for example, in the mouth and with any type of pathology of internal organs which may be treated with topical applications having the same characteristics, for example rectal applications. The Application also contains a number of examples and conclusions reached from the examples. The conclusions reached purport to suggest that the formulations are for a topical use and are successful only because of the adhesive nature of the films, prolonging the bioavailability of the medicine. In this regard see, at page 84:

> "As can be observed from the results reported in Table 2, the HYC derivatives all proved to possess a considerable anti-inflammatory activity consistently superior to that of the corresponding cortisones tested in parallel, reduced not only the percentage of eyes with phlogosis on each day of observation, but also reducing the duration of inflammation. The most efficient of these derivatives seem to be HYC4, HYC5 and HYC6, presumably because they are more lipophilic."

and at page 93:

> "The bioavailability, as compared to hydrocortisone, of the three products in examination, proves to be complete and even superior to that of the quick release preparation. Regarding this, however, the absorption is slower (maximum time about 2 hrs) and maximum concentrations equal to those of subcutaneously administered cortisol are not reached. The plasmatic cortisolemia proves however on average to be higher several hours after administration. Esterification with hyaluronic acid therefore

determines slower release of hydrocortisone, and this is the desired objective."

Note also the results discussed at page 97.

At page 103 the inventors discuss the use of esters of hyaluronic acid in which the medicines form part of the ester. One or more medicaments resulting from the association of one such esters with the pharmacologically active substance is indicated to be useful for topical application. The inventors suggest that the substances could also be used for oral, rectal, parenteral, subcutaneous, local or intradermal use. For parenteral and subcutaneous administration, the inventors purport to suggest that it is possible to use forms intended for intramuscular or intradermal administration, or suitable for infusions or intravenous injections. However the results expected are to be of the same character as those previously described in the application. The characteristics as discussed include those previously mentioned which include prolonged action, retard actions (page 19), adhesiveness (page 27), and no sensitization effects (page 27). -- Once again no effective dosage amounts are taught.

Canadian Letters Patent 1,205,031 is to the same effect as the other Fidia references discussed including U.S. Patent 4,736,024. This Canadian patent teaches processes for the manufacture of fractions of hyaluronic acid having specified molecular weights. The patent alleges the fractions of the hyaluronic acid so produced to be substantially pure and non-inflammatory (page 3(a), line 12). Beginning at page 13, the biological and pharmaceutical activity of the fractions is discussed (for example inflammation at page 16-17, lines 15-17).

Wound healing is discussed at page 18. Treatment of the joints of horses is discussed at page 19, line 11-14. Page 20 lists some pharmaceutical preparations. However these compositions do not teach Applicants' invention. They merely teach formulations (which are not dosage amounts or even a plurality of dosage amounts as used by Applicants in their method claims). Nor do they teach the use of dosage amounts of Hyaluronic Acid and a dosage amount of a medicine and/or therapeutic agent for the treatment of basal cell carcinoma.. They merely teach, in Applicants' respectful submission, combinations of hyaluronic acid (not the dosage amounts as taught by Applicants).

At page 24, reference is then made to the use of the fractions of hyaluronic acid with ophthalmic drugs-pilocarpine nitrate, triamcinolone, epidermal growth factor (EGF) and an antibiotic - spreptomcycin and gentamycin (page 24, lines 21-23). Note however though mixtures of the hyaluronic acid and medicine and therapeutic agent are made, drops are taken and instilled in the eye - these drops are instilled from a micro syringe (page 26, line 21) - 10^{-6} litres or 10^{-3} milliliters. Dosages far less than those claimed by Applicants are taught. Thus the amounts instilled will only act as a depot (as with the other Fidia references. [Applicants relate this Patent to the other Fidia references because the inventor Francesco della Valle appears to be the same inventor and the teachings are the same].

At page 30, line 2 drops are once again discussed as being administered. At page 34, line 2, drops are again discussed. At page 36, line 15, drops are discussed once again. Once again No amounts as taught by the Applicants. The drops are instilled from a microsyringe.

Thus the mixtures made in Canadian Letters Patent 1,205,031 would not constitute compositions from which dosage amounts of Applicants' invention can be withdrawn. The results are discussed at page 39, line 15 to page 40, line 13. The reason is that "the HA fractions exhibit a high level of tolerability to the eye and a high compatibility with the corneal epithelium. (Page 41, lines 31-32). The fractions do not exhibit undesirable inflammatory side reactions (Page 42, lines 5-6). There is as a result no teachings of Applicants' invention (composition claims and use claims). No effective amounts as claimed by Applicants have been taught.

The same comments are applicable to U.S. Patent 4,736,024. No dosage amounts are taught. Nor is there any teaching of their use to treat basal cell carcinoma (or any of the conditions in Applicants' Claims). Drops containing 10^{-6} litres are taught in this U.S. Patent which would contain less than the amount specified in Applicants' Claims. This patent is not relevant in the same way the Japanese Patent Application to Miyazaki is not relevant. A copy of the translation of the Japanese Application is enclosed although Applicants believe that the Examiner was forwarded a copy of the translation earlier. This translation is attached as **Schedule I**. See page 4, fifth to last line of the translation, when an injection of the medicine is gradually released from the dosage form.

> "Thus, when injection substance as gradual emission, drug is considered, the amount of administration at a time is increased. In addition, when expecting extreme gradual emission, greater amount of gradual emission material is necessary."

This is consistent through the entire teachings of the reference and culminates with the statements at page 17,

> "This means a delay of absorption of predonisolone [sic] based on the action of hyaluronic acid to cause gradual emission of predonisolone [sic]."

It is clear from the teachings that high molecular weight (a million or more daltons of hyaluronic acid) is involved. There is no dilution of the hyaluronic acid in the case of higher molecular weight amounts of hyaluronic acid as described in Applicants' Application. This reference does not teach Applicants' invention or render Applicants' invention obvious.

Consequently, not only do the references teach inventions quite foreign and removed from Applicants' teachings, they do not motivate anyone to move in the direction of Applicants' methods of treatment. The Examiner has done precisely what the law has not permitted him to do namely, he has, in hindsight, picked over the remnants of the prior art, taken parts that may in hindsight look similar to Applicants' teachings, and found Applicants' invention to be obvious by picking and choosing from the references. Furthermore, even if credence is given to the Examiner's suggestions that the references could be combined in the manner in which he has combined them (which Applicants strongly deny), nevertheless, Applicants' invention provides totally <u>unexpected</u> utility. The results are totally unexpected. Looking at the results in the Application and those of the additional tests (shown in the attached Schedules), a person skilled in the art would conclude (<u>must</u> conclude)

that for the treatment of basal cell carcinoma, the results are totally unexpected (87% response).

Some dependent claims also refer to lesser molecular weights of the form of hyaluronic acid being used. Della Valle et al may have suggested molecular weight fractions of between 50,000 to 730,000. However, Della Valle (U.S. Patent 4,736,024) did not teach sufficient amounts of hyaluronic acid in the dosage amounts. Della Valle taught drops which acted as a depot sitting on the eye.

In view of the above, Applicants respectfully submit that their Application is in condition for allowance and same is solicited at the earliest convenience. If the Examiner has any questions, he is respectfully requested to contact Ivor M. Hughes at telephone (905) 771-6414 call at convenience.

Applicants note that the Official Action was addressed to Marcelo K. Sarkis at Hughes, Etigson as the Agent of Record. Please note that Marcelo Sarkis was not appointed as the agent but, rather as an Associate Agent who is able to work on the file. Any further correspondence from the Patent Office should be addressed to Ivor M. Hughes of Hughes Etigson, 175 Commerce Valley Drive,West, Suite 200, Thornhill, Ontario L3T 7P6.

The office is thanked for its assistance.

Respectfully submitted,
HUGHES, ETIGSON

Ivor M. Hughes

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